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(71) Applicant: FISONS plc
Fison House Princes Street
Ipswich Suffolk IP1 1QH(GB)

(72) Inventor: Alsop, Ranulph Michael
28 Windemere Drive
Alderley Edge Cheshire(GB)

(72) Inventor: Forrester, Raymond Brian
7 Alderley Close
Sandbach Cheshire(GB)

(72) Inventor: Manning, David John
Hillview Under Rainow Road Timbersbrook
Congleton Cheshire(GB)

(74) Representative: Craig, Christopher Bradberry et al,
Fisons plc 12 Derby Road
Loughborough Leicestershire LE11 0BB(GB)

(54) Polymers for use in continuous peritoneal dialysis.

(57) There is described polysaccharides of high molecular weight for use in peritoneal dialysis. The polysaccharides are capable of dialysing human serum for long periods of time without causing damage to the peritoneum and are also capable of preventing loss of polymer from the peritoneum to the serum.

There is also described a method of making the polysaccharides and pharmaceutical formulations containing them.

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This invention relat s to a new form of polymer, a method for its production and compositions containing it.

Maltodextrins (glucose polymers) are produced by the hydrolysis of pure starch isolated from various natural products, e.g. wheat, rice, tapioca etc. In a typical process a pure isolated starch is produced by a multi-stage separation process involving removal of protein, oil, fibre and glutens before being hydrolysed.

As no single number can adequately characterise the molecular weight of a polymer, such as a maltodextrin, various averages are used. The most commonly used are the weight average molecular weight ($\bar{M}_w$) and the number average molecular weight ($\bar{M}_n$):

$$\bar{M}_w = \frac{\sum n_i M_i^2}{\sum n_i M_i}$$

$$\bar{M}_n = \frac{\sum n_i M_i}{\sum n_i}$$

where n_i is the number of molecules of molecular weight M_i. $\bar{M}_w$ is particularly sensitive to changes in the high-molecular-weight content of the maltodextrin polymer whilst $\bar{M}_n$ is largely influenced by changes in the low molecular weight of the sample.

We have now found that it is possible to monitor

starch hydrolysis and in particular to stop the hydrolytic action when the hydrolysate contains the maximum amount of molecules in the desired molecular weight range. The monitoring may be carried out by a technique known as size exclusion chromatography. Furthermore, fractionation of the starch hydrolysate can be monitored by size exclusion chromatography and a weight average molecular weight, a number average molecular weight and a molecular weight distribution of the products can be determined using chromatographic columns calibrated with dextran standards (Alsop et al Process Biochem 2 10-15 (1977) and Alsop et al J. Chromatography 246, 227-240, (1982)).

We have also found a method for optimising the yield of a glucose polymer with a preselected molecular weight range.

Glucose polymers are often characterised by the expression "degree of polymerisation" (DP). In this terminology a product may be described as having 20% of its weight comprising molecules with a DP greater than 10, ie. 20% has a molecular weight greater than 1656 (a polymer comprising 10 glucose units).

British Patent Application 2132914A describes a glucose polymer mixture having at least 15% by weight of glucose polymers of DP greater than 12 for use in continuous ambulatory peritoneal dialysis (CAPD). PCT/US

Application 82/00774 describes a CAPD solution comprising glucose polymers of DP of at least 4.

European Patent Application 0076355 A2 discloses glucose polymer mixtures having at least 99% of glucose polymers of DP less than 12 for use in CAPD.

It has now surprisingly been found that certain polydisperse glucose polymer mixtures of high molecular weight are useful in medicine, e.g. in CAPD and in prevention of post-operative adhesions.

According to the invention we provide a glucose polymer (I), wherein at least 50% by weight of the polymer is of molecular weight in the range 5000 to 30000.

We particularly prefer a glucose polymer (I), wherein at least 80% by weight of the polymer is of molecular weight in the range 5000 to 50,000.

We prefer the glucose polymer (I) to have a weight average molecular weight in the range of from 5000 to 100000, preferably of from 5000 to 50000, more preferably of from 12000 to 25000, and most preferably of from 14000 to 20000.

We prefer the glucose polymer (I) to have a number average molecular weight of less than 8000, preferably less than 5000, more preferably less than 4000 and most preferably less than 2900.

We prefer the content of mono-, di-, and

tri-saccharide compounds present in the glucose polymer (I) to be less than 5% by weight, more preferably less than 2% and most preferably 0% by weight. By 0% we mean an amount which is undetectable by conventional methods.

We further prefer that the content of glucose polymers with molecular weight greater than 100000 in the glucose polymer (I) should be less than 5%, preferably less than 3% and most preferably less than 1% by weight.

We prefer the glucose polymers to be substantially free from endotoxins and nitrogenous contaminants arising from the original starch, or from the enzyme preparations used for its hydrolysis.

We particularly prefer the endotoxin level to be less than 0.25 endotoxin units/ml, more preferably less than 0.12 endotoxin units/ml and most preferably less than 0.06 endotoxin units/ml as determined by the Limulus Lysate Test (US Pharmacopoeia).

We prefer the nitrogen content of the glucose polymers to be less than 0.01% w/w, more preferably less than 0.001% w/w and most preferably zero as determined by the Kjeldahl method (British Pharmacopoeia)

We also prefer the glucose polymers to be substantially free of undesirable metals, e.g. aluminium. Thus we prefer the level of aluminium to be less than 500 ppb, more preferably less than 200 ppb and most preferably

less than 100 ppb.

We also prefer an aqueous solution comprising 10% w/v of the glucose polymer to be substantially clear and colourless. Thus we prefer such a solution to have a turbidity value of less than 30 EEL units (US Pharmacopoeia), more preferably less than 20 EEL units and most preferably less than 10 EEL units. We also prefer such a solution to have no substantially visible colour. We particularly prefer the solution to have a visible colour of less than 10 APHA Hazen units and more preferably less than 5 APHA Hazen units. The content of colour precursors such as 5-hydroxymethyl furfural can be measured by absorption of ultraviolet light of wavelength 275 or 284nm. We prefer the absorbance to be less than 0.5, more preferably less than 0.25 and most preferably less than 0.15. The transmission of ultraviolet light measured at a wavelength of 430 nm is preferably greater than 90% and more preferably greater than 95%.

It is a further feature of this invention to provide a glucose polymer (I) having up to 20% by weight of glucose polymers with a molecular weight of from 800 to 10,000, preferably of from 1500 to 4000. We particularly prefer a glucose polymer (I) having up to 20% by weight of glucose polymers with a molecular weight of from 1500 to 2500, more preferably up to 10% by weight and most

preferably up to 7% by weight.

According to the invention we also provide a method for the production of a glucose polymer (I), which comprises

a) fractional precipitation of an aqueous solution of a glucose polymer containing polymer (I) with a water miscible solvent, and/or

b) filtration of an aqueous solution of a glucose polymer containing polymer (I) through membranes possessing an appropriate molecular weight cut-off range. The molecular weight cut-off range may be determined empirically.

In process a) the process parameters used are interdependent and each parameter may vary depending upon the desired quality of the product, the desired molecular weight range, etc. The water miscible solvent may be an alcohol, eg an alkanol, such as ethanol. The solvent may be present in an aqueous solution which is mixed with an aqueous glucose polymer. The concentration of the solvent in the aqueous solution before mixing may be from 60 to 100%v/v, preferably from 75 to 90%v/v, and most preferably about 85%v/v.

The concentration of the aqueous glucose polymer solution before mixing may be from 0 to 80% w/v, preferably from 15 to 65% w/v, and most preferably from 30

to 40% w/v.

The fractionation may be carried out at a temperature of from 10 to 40°C and more preferably from 20 to 30°C.

In process b) the type of membrane material used may vary with the particular molecular weight distribution which is desired. A chemically inert plastics material may be used for the membrane, eg. a cellulose acetate or polytetrafluoro-ethylene. We particularly prefer to use a material which is mechanically stable at high temperatures and pressures, eg. a polysulphone.

A series of membranes may be used consecutively such that both a high and a low molecular weight fractionation is carried out. The membrane fractionation may be carried out at elevated temperature sufficient to prevent bacteriological contamination. We prefer the fractionation to be carried out at a temperature of from 0 to 90°C, preferably from 20 to 80°C, and most preferably from 65° to 75°C.

The feed solution may be of a concentration of from 1.0 to 30.0% w/v, preferably from 5 to 15% w/v and most preferably about 10% w/v.

The glucose polymer starting material is preferably prepared by a method, e.g. hydrolysis, designed to optimise the proportion of polymer (I), and the progress of that method is preferably monitored by size exclusion

chromotography. Any starch may be used in the hydrolysis but we prefer to use a cornstarch.

The molecular weight distribution of the fractions may be determined using the chromatographic techniques described by Alsop et al J. Chromatography 246, 227-240 (1982). The optical rotation of the various solutions produced may also be used to identify the concentrations of the polymer contained by the solutions.

The high molecular weight waste products from the fractionations may be further hydrolysed to produce further quantities of lower molecular weight products which can be fractionated. The low molecular weight waste products may be useful in the production of glucose syrups.

Before, during and/or after the fractionation of process a) or b) the polymer may be purified. The purification may be to remove undesirable colour or to remove contaminants, for example proteins, bacteria, bacterial toxins, fibres or trace metals, eg aluminium. Any conventional purification technique may be applied, for example, filtration and/or absorption/adsorption techniques such as ion exchange or charcoal treatment.

The product of the fractionation of process a) or b) may be packaged and transported as a syrup or solution, for example an aqueous solution. However, we prefer the product to be in a solid form, preferably a powder, and

most preferably spray dried granules.

The glucose polymer (I) is useful in a wide variety of medical indications, e.g. peritoneal dialysis, as a nutritional agent or for the prevention of post-operative adhesions etc.

According to the invention we also provide a pharmaceutical composition comprising a glucose polymer (I), wherein at least 50% of the polymer is of a molecular weight in the range 5000 to 30000, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Any composition for use in CAPD preferably comprises physiologically acceptable electrolytes, eg. sodium, potassium, calcium and magnesium in order to prevent the transfer of desirable electrolytes from the serum to the peritoneum. The amounts may vary depending upon the requirements of any individual patient and are generally sufficient to provide an osmolarity of from about 240 to 275 mOsm/litre (see Example A).

According to the invention we also provide a physiologically acceptable polysaccharide (II) with an osmolarity of less than 160 mOsm/litre, preferably less than 110 mOsm/litre more preferably less than 90 mOsm/litre and most preferably less than 20 mOsm/litre, which is capable of being used in solution in the dialysis of normal human serum. By normal human serum we mean

serum with an osmolarity of between 280 and 290 mOsm/litre at 37°C. The polysaccharide (II) preferably has the molecular weight and other parameters described above with respect to glucose polymer (I). Any suitable polysaccharide may be used but we prefer the polysaccharide to be a glucose polymer (I).

The polysaccharide (II) may be prepared by any of the processes hereinbefore described or by conventional processes known per se.

We also provide a composition capable of dialysing normal human serum comprising a polysaccharide (II) and having an osmolarity somewhat greater than normal serum. The osmolarity of the composition is preferably less than 400 mOsm/litre, more preferably less than 350 mOsm/litre and most preferably less than 330 mOsm/litre at 37°C. We particularly prefer a composition with an osmolarity less than 300 mOsm/litre at 37°C.

The composition may be in solid form, eg suitable for extemporaneous production of a solution, or it may be a liquid, eg in the form of an aqueous solution. The composition preferably includes pharmacologically acceptable electrolytes. Such electrolytes may include appropriate ions , eg of sodium, potassium, calcium, magnesium and chloride; buffers, eg. lactate, acetate or bisulphite; or other additives, such as amino acids,

polyols or insulin.

The polymer (I) and the polysaccharide (II) are advantageous over the prior art. The long term use of high osmolarity glucose solutions in peritoneal dialysis can result in irreversible changes to the peritoneal membrane due to the continuous high pressure differentials across the peritoneum. When a glucose solution with a low osmolarity is used in CAPD for greater than four hours glucose may be lost from the peritoneum to the serum, this is undesirable, particularly in diabetic patients. The present invention provides a method of applying an osmotic pressure over the peritoneum for greater than four hours without causing damage to the peritoneum whilst preventing appreciable loss of polysaccharide to the serum from the peritoneum and maintaining the flow of water from the serum to the peritoneum.

The invention will now be described by way of example only and by reference to the attached drawings in which Figure 1 is a flow diagram of the process described in Example 1;

Figure 2 is a flow diagram of the process described in Example 2;

Figure 3 is a flow diagram of the process described in Example 3;

Figure 4 is a flow diagram of the process described

in Example 4; and

Figure 5 is a flow diagram of the process described in Example 5.

In the Examples OR means optical rotations.

The molecular weight distribution of the starch hydrolysate starting material which was used in Examples 1 and 2 is shown in Table 1. The starting material was found to have an $\bar{M}_w$ of 6309 and an $\bar{M}_n$ of 401.

Example 1

Ethanol Fractionation

The fractionation procedure used to isolate the required molecular weight distribution of a maltodextrin syrup is given in Figure 1. The precise technique to be used will of course be varied to take account of the quality and molecular weight distribution of the maltodextrin used as the starting material.

Aqueous ethanol (33 l at 85%v/v) was added, with stirring, to 37 l of a maltodextrin syrup (at 116°OR=23kg, dissolved maltodextrins). After settling the resulting Syrup I (5 l at 92° OR) was drawn from the bottom outlet of the fractionator.

Aqueous ethanol (40 l at 85% v/v) was added, with stirring, to the Supernatant I. After settling the Supernatant II (84 l at 13.5° OR) was decanted.

Aqueous ethanol (75 l at 85% v/v) and pyrogen free

water (25 l) were added, with stirring, to the Syrup II (46 l at 50.25° OR). After settling the Supernatant III (103 l at 3.5° OR) was decanted.

Aqueous ethanol (54 l at 85% v/v) and pyrogen free water (14 l) were added, with stirring, to the resulting Syrup III (13 l at 104° OR). After settling the Supernatant IV (69 l at 3.4° OR) was decanted.

Aqueous ethanol (48 l at 85% v/v) and pyrogen free water (12 l) were added with stirring, to the resulting Syrup IV (12 l at 98° OR). After settling the required maltodextrin fraction, Syrup V, (10.5l at 102.4° OR ≡ 5.5kg dissolved maltodextrins) was drawn off. This represents 23.9% recovery of the maltodextrins present in the initial syrup. 3.8kg of Syrup V was dissolved in pyrogen free water (25 l) and refluxed with stirring in the presence of 0.4kg of activated carbon (Norit UK, GSX grade). The carbon was removed by filtration and the resulting syrup was used to prepare peritoneal dialysis solutions.

The $\bar{M}_w$ of the product maltodextrin after carbon treatment was 18949 and the $\bar{M}_n$ was 6316. The molecular weight distribution is shown in Table 2, 61% of the product lies within the range 5000 to 30000.

Example 2

Ethanol Fractionation

The procedure of Example 1 was repeated using the quantities shown in Figure 2. However, the carbon treatment was carried out by adding the activated carbon (Norit UK, grade GSX 5kg) to the alcoholic Syrup V. The alcohol was removed by steam distillation and the carbon by depth filtration (Carlson Ford grade NA90). The resulting syrup was then spray dried.

The $\overline{M}_w$ of the product maltodextrin was 12027 and the $\overline{M}_n$ was 3447. The molecular weight distribution is shown in Table 3, 60% of the product lies within the range 5000 to 30000.

The $\overline{M}_w$ of the product maltodextrin after carbon treatment was 12027 and the $\overline{M}_n$ was 3447. The molecular weight distribution is shown in Table 3, 60% of the product lies within the range 5000 to 30000.

Example 3

Ethanol Fractionation

The molecular weight distribution of the starting material is shown in Table 4. The starting material had an $\overline{M}_w$ of 11534 and an $\overline{M}_n$ of 586.

The procedure of Example 1 was repeated using the quantities shown in Figure 3. However, the carbon treatment was carried out by adding the activated carbon (Norit UK, Grade GSX 60kg) to the alcoholic syrup IV. The activated carbon was filtered off by depth filtration

(Carlson Ford Grade 'O' pads). A further carbon treatment was carried out on the syrup VI (15kg Norit UK Grade GSX, filtered off using Carlson Ford Grade NA90 pads) during ethanol removal by steam distillation. The ethanol-free syrup was spray dried.

The $\bar{M}_w$ of the product maltodextrin was 21838 and the $\bar{M}_n$ was 7105. The molecular weight distribution is shown in Table 5, 58% of the product lies within the range 5000 to 30000.

Example 4

Ethanol Fractionation

The molecular weight distribution of the starting material is shown in Table 6. The starting material had an $\bar{M}_w$ of 12636 and an $\bar{M}_n$ of 639.

The procedure of Example 1 was repeated using the quantities shown in Figure 5. The carbon treatment was carried out by adding activated carbon (Norit UK, Grade GSX, 20kg) to the alcoholic syrup IV. The carbon was filtered by depth filtration (Carlson Ford Grade 'O' pads). Ethanol was removed from the final syrup (syrup V) by steam distillation and the aqueous product ion exchanged (mixed bed system), and spray dried. The mixed bed resin was Duolite A1725 in the hydroxyl form and C225H in the chloride form. (Duolite is a trade mark).

The $\bar{M}_w$ of the product maltodextrin was 22020 and

The $\bar{M}_n$ was 7767. The molecular weight distribution is shown in Table 7, 60% of the product lies within the range 5000 to 30000.

Example 5

Membrane Fractionation

a) A high molecular weight fractionation was carried out by passing 1.9kg of starch hydrolysate, (molecular weight distribution, see Table 8), as a 10% w/v solution (20 litres) through a series of membranes. Polysulphone membranes with an approximate molecular weight cut-off of 20,000 and an area of $0.216m^2$ were used. The feed flowrate was 6.6 litres/min at a temperature of 70^oC. The total solids level of the retained liquid was maintained at 10% w/v and the low molecular weight species were washed through the membrane. After 6.5 hours the concentration of carbohydrate in the permeate product stream leaving the ultrafiltration module was low, eg 0.5% w/v, (see Table 9) and the process was terminated. The high molecular weight residues were recovered from the membrane (0.2kg, 10.5%) and the permeative low molecular weight product was isolated from the permeate (1.70kg, 89.5%).

The molecular weight distribution of the product is shown in Table 10.

b) A low molecular weight fractionation was carried out

by passing 0.64kg of the low molecular weight product from Example 3a) as a 3.2% w/v solution (20 litres) through a series of membranes. Polysulphone membranes with an approximate molecular weight cut-off of 2,000 and an area of 0.18m^2 were used. The feed flowrate was 6.6 litres/min at a temperature of 70°C. The total solids level of the retained liquid was maintained at approximately 4.0% w/v and the low molecular weight species were washed through the membrane. After 95 minutes the concentration of carbohydrate in the permeate stream was zero (see Table 11) and the process was terminated. The undesired permeate product was recovered (0.465kg, 73%) and the desired retained product was 0.166kg (26%).

The molecular weight distribution of the product is shown in Table 12, 55% of the product lies within the range 5000 to 30000.

Example 6

a) Membrane Fractionation

The procedure for Example 5 a) was repeated using 2.0kg of starch hydrolysate. Membranes were used with a cut-off value of 25000 an area of 0.144m^2. After 5.5 hours the concentration of the carbohydrate in the permeate was undetectable (see Table 13). The high molecular weight residues were recovered from the membrane

(0.384kg, 19.2%) and the permeative low molecular weight product was isolated from the permeate (1.613kg, 80.6%). The molecular weight distribution of the permeate is given in Table 14. $\bar{M}_w$ was found to be 4906 and $\bar{M}_n$ determined as 744.

b) Ethanol Fractionation

1.7kg of maltodextrin from Example 6a) in 53 litres of pyrogen free water was mixed with 132.5 litres of aqueous ethanol (85% v/v).

The syrup from the fractionation had an $\bar{M}_w$ of 19712 and an $\bar{M}_n$ of 4798. The molecular weight distribution is shown in Table 15, 55% of the product lies within the range 5000 to 30000.

Example 7

Ethanol Fractionation

The procedure of Example 3 was carried out. Syrup V was isolated and the molecular weight distribution determined.

The $\bar{M}_w$ of the product maltodextrin was 20211 and the $\bar{M}_n$ was 2890. The molecular weight distribution is shown in Table 16, 50% of the product lies within the range 5000 to 30000.

Example A

Two examples of peritoneal dialysis solutions are shown below. The ionic electrolytes behave ideally and therefore 1 mOsm/l is equivalent to 1 mmol/l.

	1	2
Sodium (mOsm/l)	131	138
Potassium (mOsm/l)	0	0
Calcium (mOsm/l)	1.8	1.78
Magnesium (mOsm/l)	0.75	0.75
Chloride (mOsm/l)	91	90
Lactate (mOsm/l)	45	45
Acetate (mOsm/l)	-	-
Bisulphite (mOsm/l)	-	-
Total Electrolyte Osmolarity (mOsm/l)	269.6	275.5
Glucose polymer (I) (mOsm/l)	12.9 (50g/l)	12.9 (50g/l)
Total Osmolarity	282.5	288.4

Table 1

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
165	0.00
167	2.50
172	5.00
178	7.50
184	10.00
191	12.50
199	15.00
207	17.50
216	20.00
226	22.50
237	25.00
249	27.50
262	30.00
276	32.50
291	35.00
307	37.50
326	40.00
346	42.50
366	45.00
391	47.50
419	50.00
446	52.50
488	55.00
532	57.50
598	60.00
681	62.50
837	65.00
1099	67.50
1570	70.00
2328	72.50
3436	75.00
4915	77.50
6789	80.00
7135	82.50
12074	85.00
13825	87.50
20735	90.00
27447	92.50
37044	95.00
53463	97.50
199559	100.00

Table 2

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
296	0.00
1231	2.50
1756	5.00
2279	7.50
2795	10.00
3291	12.50
3771	15.00
4246	17.50
4722	20.00
5203	22.50
5696	25.00
6196	27.50
6718	30.00
7247	32.50
7809	35.00
8378	37.50
8986	40.00
9607	42.50
10272	45.00
10960	47.50
11695	50.00
12472	52.50
13295	55.00
14184	57.50
15126	60.00
16162	62.50
17274	65.00
18499	67.50
19872	70.00
21352	72.50
23122	75.00
25084	77.50
27319	80.00
30070	82.50
33400	85.00
37527	87.50
42867	90.00
50412	92.50
61686	95.00
82648	97.50
288182	100.00

Table 3

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
183	0.00
484	2.50
874	5.00
1292	7.50
1695	10.00
2082	12.50
2460	15.00
2836	17.50
3215	20.00
3595	22.50
3986	25.00
4382	27.50
4786	30.00
5204	32.50
5627	35.00
6072	37.50
6519	40.00
6994	42.50
7473	45.00
7982	47.50
8499	50.00
9048	52.50
9611	55.00
10212	57.50
10836	60.00
11502	62.50
12208	65.00
12955	67.50
13777	70.00
14637	72.50
15626	75.00
16708	77.50
17905	80.00
19298	82.50
20957	85.00
22960	87.50
25476	90.00
29002	92.50
34287	95.00
44550	97.50
299523	100.00

Table 4

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
146	0.00
157	2.50
173	5.00
192	7.50
213	10.00
235	12.50
259	15.00
285	17.50
313	20.00
343	22.50
378	25.00
411	27.50
450	30.00
489	32.50
536	35.00
583	37.50
636	40.00
695	42.50
755	45.00
837	47.50
920	50.00
1036	52.50
1161	55.00
1350	57.50
1590	60.00
1919	62.50
2393	65.00
3094	67.50
4176	70.00
5731	75.00
7802	75.00
10354	77.50
13393	80.00
17014	82.50
21436	85.00
27030	87.50
34348	90.00
44586	92.50
60087	95.00
89965	97.50
578156	100.00

Table 5

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
1394	2.50
2060	5.00
2644	7.50
3199	10.00
3751	12.50
4299	15.00
4856	17.50
5421	20.00
6003	22.50
6597	25.00
7208	27.50
7841	30.00
8497	32.50
9175	35.00
9881	37.50
10615	40.00
11385	42.50
12189	45.00
13033	47.50
13924	50.00
14870	52.50
15874	55.00
16947	57.50
18096	60.00
19333	62.50
20685	65.00
22167	67.50
23793	70.00
25616	72.50
27661	75.00
29973	77.50
32624	80.00
35745	82.50
39445	85.00
44003	87.50
49720	90.00
57401	92.50
68831	95.00
90432	97.50

Table 6

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
146	0.00
156	2.50
175	5.00
197	7.50
223	10.00
250	12.50
279	15.00
311	17.50
345	20.00
381	22.50
420	25.00
462	27.50
506	30.00
555	32.50
603	35.00
662	37.50
721	40.00
792	42.50
875	45.00
971	47.50
1099	50.00
1269	52.50
1496	55.00
1827	57.50
2320	60.00
3043	62.50
4107	65.00
5556	67.50
7396	70.00
9581	75.00
12065	75.00
14880	77.50
18153	80.00
21986	82.50
26590	85.00
32293	87.50
39532	90.00
49285	92.50
63509	95.00
89961	97.50
439968	100.00

Table 7

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
1586	2.50
2290	5.00
2882	7.50
3443	10.00
3991	12.50
4545	15.00
5110	17.50
5694	20.00
6302	22.50
6931	25.00
7587	27.50
8263	30.00
8965	32.50
9692	35.00
10441	37.50
11218	40.00
12030	42.50
12878	45.00
13761	47.50
14691	50.00
15671	52.50
16705	55.00
17805	57.50
18982	60.00
20244	62.50
21615	65.00
23120	67.50
24766	70.00
26584	72.50
28624	75.00
30930	77.50
33568	80.00
36623	82.50
40240	85.00
44626	87.50
50148	90.00
57346	92.50
67788	95.00
86399	97.50

Table 8

Starch Hydrolysate
Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
146	0.00
160	2.50
176	5.00
195	7.50
217	10.00
240	12.50
264	15.00
291	17.50
322	20.00
354	22.50
390	25.00
428	27.50
470	30.00
511	32.50
558	35.00
605	37.50
657	40.00
714	42.50
772	45.00
852	47.50
934	50.00
1050	52.50
1185	55.00
1398	57.50
1688	60.00
2104	62.50
2708	65.00
3617	67.50
4870	70.00
6517	75.00
8552	75.00
10946	77.50
13729	80.00
17036	82.50
21022	85.00
25964	87.50
32324	90.00
40911	92.50
53516	95.00
76329	97.50
356145	100.00

Table 9

Time	Pressure in Bar	Pressure out Bar	Temp °C	Permeate Flow Rate l/min	Feed Soln Concn % w/v	Permeate Conc % w/v
0	4.6	3.4	64	on total recycle		
1	"	"	64	190	10.5	7
1.5	"	"	68	192	10	6.5
2	"	"	71	198	9	5
3	"	"	69	166	8	3.5
4	"	"	69	165	6.75	2.25
6	"	"	70	148	6	1
6.5	"	"	65	140	8	0.5

Table 10

Permeate (Ex 5(a))
Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
146	0.00
169	2.50
205	5.00
247	7.50
285	10.00
323	12.50
362	15.00
403	17.50
444	20.00
488	22.50
533	25.00
581	27.50
630	30.00
681	32.50
734	35.00
787	37.50
845	40.00
906	42.50
966	45.00
1038	47.50
1117	50.00
1196	52.50
1303	55.00
1423	57.50
1567	60.00
1758	62.50
2003	65.00
2308	67.50
2720	70.00
3287	72.50
4080	75.00
5156	77.50
6535	80.00
8280	82.50
10326	85.00
12731	87.50
15631	90.00
19283	92.50
24378	95.00
32986	97.50
93587	100.00

Table 11

Time	Pressure in Bar	Pressure out Bar	Temp °C	Permeate Flow Rate l/min	Feed Soln Concn % w/v	Permeate Conc % w/v
0	5.4	4.6	70	390	3.25	1.75
15 mins	5.4	4.6	70	400	3.5	1.5
35 mins	5.4	4.6	71	300	5.0	2.0
60 mins	5.4	4.6	70	280	4.25	1
95 mins	5.4	4.6	69	280	3.0	0

Table 12

Retentate (Ex 5(b))
Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
186	0.00
834	2.50
1339	5.00
1837	7.50
2410	10.00
3090	12.50
3869	15.00
4717	17.50
5613	20.00
6540	22.50
7492	25.00
8458	27.50
9433	30.00
10414	32.50
11398	35.00
12385	37.50
13374	40.00
14384	42.50
15406	45.00
16449	47.50
17519	50.00
18611	52.50
19754	55.00
20917	57.50
22167	60.00
23437	62.50
24832	65.00
26283	67.50
27852	70.00
29576	72.50
31415	75.00
33457	77.50
35747	80.00
38449	82.50
41731	85.00
45703	87.50
50765	90.00
57945	92.50
69100	95.00
90766	97.50
410452	100.00

Table 13

Time	Pressure in Bar	Pressure out Bar	Temp °C	Permeate Flow Rate l/min	Feed Soln Concn % w/v	Permeate Conc % w/v
0.75	4.7	3.3	67	225	9.5	5.0
1.25	4.7	3.8	68	184	10.5	5.5
2.50	4.8	3.2	70	150	9.0	4.0
3.50	4.8	3.2	70	144	8.0	1.5
4.50	4.8	3.2	69	130	6.5	0.5
5.50	4.8	3.2	69	123	6.0	0

Table 14

Permeate (Ex 6)
Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
146	0.00
170	2.50
207	5.00
251	7.50
293	10.00
335	12.50
378	15.00
423	17.50
469	20.00
516	22.50
566	25.00
616	27.50
660	30.00
720	32.50
773	35.00
827	37.50
882	40.00
939	42.50
1004	45.00
1070	47.50
1135	50.00
1226	52.50
1320	55.00
1418	57.50
1567	60.00
1717	62.50
1947	65.00
2218	67.50
2566	70.00
3056	72.50
3718	75.00
4671	77.50
5959	80.00
7656	82.50
9753	85.00
12271	87.50
15332	90.00
19237	92.50
24688	95.00
34400	97.50
98105	100.00

Table 15

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
170	0.00
845	2.50
1292	5.00
1674	7.50
2044	10.00
2429	12.50
2841	15.00
3283	17.50
3754	20.00
4269	22.50
4805	25.00
5361	27.50
5958	30.00
6583	32.50
7232	35.00
7937	37.50
8666	40.00
9447	42.50
10273	45.00
11129	47.50
12062	50.00
13024	52.50
14053	55.00
15147	57.50
16281	60.00
17537	62.50
18860	65.00
20264	67.50
21839	70.00
23542	72.50
25408	75.00
27488	77.50
29900	80.00
32694	82.50
36020	85.00
40183	87.50
45419	90.00
52731	92.50
64063	95.00
85249	97.50
349210	100.00

Table 16

Molecular Weight Distribution

MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
147	0.00
354	2.50
627	5.00
918	7.50
1243	10.00
1602	12.50
1996	15.00
2431	17.50
2908	20.00
3428	22.50
3990	25.00
4591	27.50
5232	30.00
5924	32.50
6653	35.00
7417	37.50
8230	40.00
9092	42.50
9990	45.00
10946	47.50
11966	50.00
13032	52.50
14178	55.00
15407	57.50
16704	60.00
18105	62.50
19643	65.00
21999	67.50
23093	70.00
25087	72.50
27332	75.00
29844	77.50
32692	80.00
35966	82.50
39805	85.00
44449	87.50
50079	90.00
57437	92.50
67881	95.00
86087	97.50
331467	100.00

What we claim is:-

1. A glucose polymer (I), characterised in that at least 50% by weight of the polymer is of a molecular weight in the range of from 5,000 to 30,000.

2. A physiologically acceptable polysaccharide (II), characterised in that it has an osmolarity of less than 160 mOsm/litre and is capable of being used to dialyse normal human serum.

3. A polymer according to either of Claims 1 or 2, characterised in that the polymer has a weight average molecular weight ($\bar{M}_w$) of from 5,000 to 50,000.

4. A polymer according to any one of the preceding claims, characterised in that the polymer has a number average molecular weight ($\bar{M}_n$) of less than 8,000.

5. A polymer according to any one of the preceding claims, characterised in that it possesses at least one of the following properties:

a) a mono-, di- and tri-saccharide content of less than 5% by weight,

b) a content of glucose polymers with molecular weight greater than 100,000 of less than 5% by weight,

c) an endotoxin level of less than 0.25 endotoxin units/ml,

d) a nitrogen content of less than 0.01% w/w,

e) an aluminium level of less than 500 ppb,

f) a turbidity value of less than 30 EEL units in a 10% w/v aqueous solution,

g) a visible colour of less than 10 APHA Hazen units in a 10% w/v aqueous solution, and

h) an absorbance of less than 0.5 when measured at either 275 or 284nm.

6. A polymer according to any one of the preceeding claims, characterised in that it is a glucose polymer having up to 20% by weight of its molecules of a molecular weight of from 800 to 10,000.

7. A method of production of a polymer according to any one of Claims 1 to 6, characterised in that the process comprises,

a) fractional precipitation of an aqueous solution of a polymer with a water miscible solvent, and/or

b) filtration of an aqueous solution of a polymer through membranes possessing an appropriate molecular weight cut-off range.

8. A pharmaceutical composition comprising a polymer according to any one of Claims 1 to 6, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A composition according to Claim 8 which possesses an osmolarity of less than 400 mOsm/litre and is capable of dialysing normal human serum.

10. The use of a polymer according to any one of Claims 1

to 6 as a pharmaceutical.

11. The use of a polymer according to any one of Claims 1 to 6 to make a solution for the dialysis of human serum.

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Claims for Austria

What we claim is:-

1. A process for the preparation of a physiologically acceptable polysaccharide (II), having an osmolarity of less than 160 mOsm/litre and capable of being used to dialyse normal human serum, characterised in that the process comprises,

a) fractional precipitation of an aqueous solution of a polymer with a water miscible solvent, and/or

b) filtration of an aqueous solution of a polymer through membranes possessing an appropriate molecular weight cut-off range.

2. A process according to Claim 1, wherein the polysaccharide (II) is a glucose polymer (I), wherein at least 50% by weight of the polymer is of a molecular weight in the range of from 5,000 to 30,000.

3. A process according to either of Claims 1 or 2, wherein the polysaccharide (II) is a glucose polymer (I) having a weight average molecular weight ($\bar{M}_w$) of from 5,000 to 50,000.

4. A process according to any one of the preceding claims, wherein the polysaccharide (II) is a glucose polymer (I) having a number average molecular weight ($\bar{M}_n$) of less than 8,000.

5. A process according to any one of the preceding claims wherein the polysaccharide (II) is a glucose

polymer (I) having a mono-, di-, and tri-saccharide content of less than 5% by weight.

6. A process according to any one of the preceding claims, wherein the polysaccharide (II) is a glucose polymer (I) having at least one of the following properties:

a) a content of glucose polymers with molecular weight greater than 100,000 of less than 5% by weight,

b) an endotoxin level of less than 0.25 endotoxin units/ml,

c) a nitrogen content of less than 0.01% w/w,

d) an aluminium level of less than 500 ppb,

e) a turbidity value of less than 30 EEL units in a 10% w/v aqueous solution,

f) a visible colour of less than 10 APHA Hazen units in a 10% w/v aqueous solution, and

g) an absorbance of less than 0.5 when measured at either 275 or 284nm.

7. A process according to any one of the preceeding claims, wherein the polysaccharide (II) is a glucose polymer (I) having up to 20% by weight of its molecules of a molecular weight of from 800 to 10,000.

8. A process according to any one of the preceding claims characterised in that the process comprises preparation of a polymer in a solid form.

9. A process according to any one of the preceding claims wherein the polysaccharide (II) is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier to provide a composition which possesses an osmolarity of less than 400 mOsm/litre and is capable of dialysing normal human serum.

10. A process according to Claim 9 wherein the pharmaceutically acceptable adjuvant is selected from sodium, potassium, calcium, magnesium, chloride, lactate, acetate, bisulphite ions; amino acids, polyols and insulin.

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Fig.1.

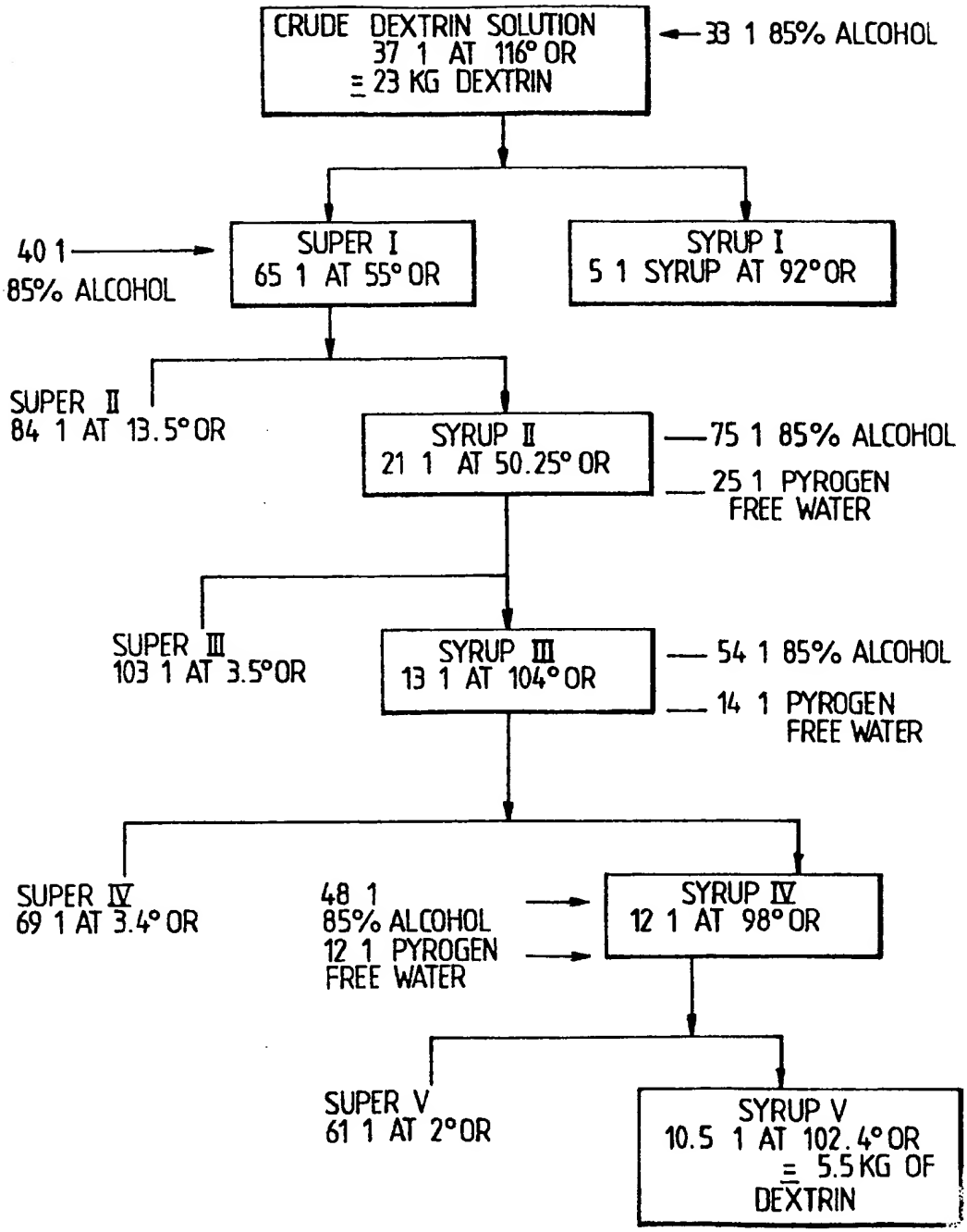

CRUDE DEXTRIN SOLUTION
37 1 AT 116° OR
≙ 23 KG DEXTRIN
33 1 85% ALCOHOL
40 1
85% ALCOHOL
SUPER I
65 1 AT 55° OR
SYRUP I
5 1 SYRUP AT 92° OR
SUPER II
84 1 AT 13.5° OR
SYRUP II
21 1 AT 50.25° OR
75 1 85% ALCOHOL
25 1 PYROGEN FREE WATER
SUPER III
103 1 AT 3.5° OR
SYRUP III
13 1 AT 104° OR
54 1 85% ALCOHOL
14 1 PYROGEN FREE WATER
SUPER IV
69 1 AT 3.4° OR
48 1
85% ALCOHOL
12 1 PYROGEN
FREE WATER
SYRUP IV
12 1 AT 98° OR
SUPER V
61 1 AT 2° OR
SYRUP V
10.5 1 AT 102.4° OR
≙ 5.5 KG OF DEXTRIN

Fig. 2.

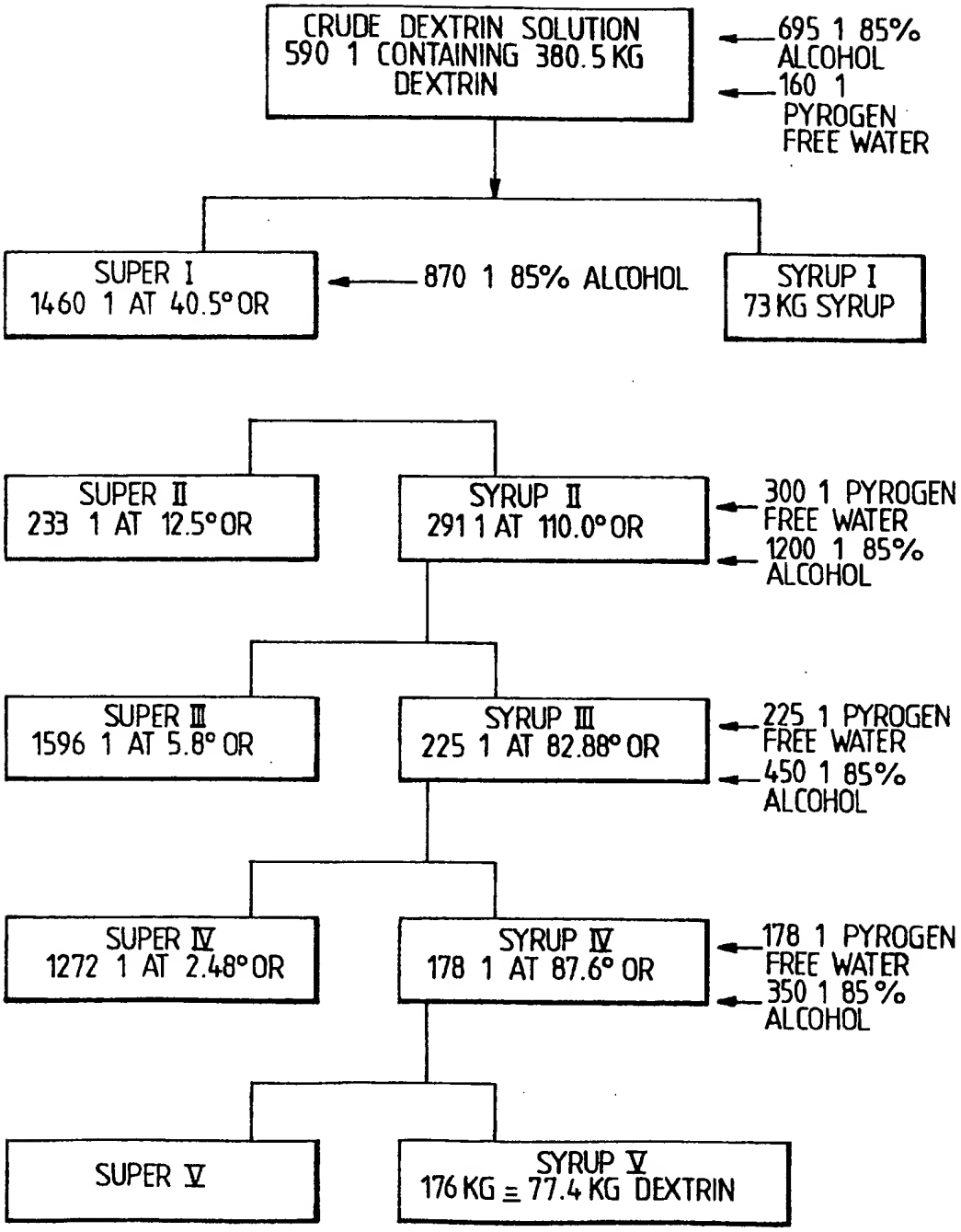

CRUDE DEXTRIN SOLUTION
590 1 CONTAINING 380.5 KG
DEXTRIN
695 1 85%
ALCOHOL
160 1
PYROGEN
FREE WATER
SUPER I
1460 1 AT 40.5° OR
870 1 85% ALCOHOL
SYRUP I
73 KG SYRUP
SUPER II
233 1 AT 12.5° OR
SYRUP II
291 1 AT 110.0° OR
300 1 PYROGEN
FREE WATER
1200 1 85%
ALCOHOL
SUPER III
1596 1 AT 5.8° OR
SYRUP III
225 1 AT 82.88° OR
225 1 PYROGEN
FREE WATER
450 1 85%
ALCOHOL
SUPER IV
1272 1 AT 2.48° OR
SYRUP IV
178 1 AT 87.6° OR
178 1 PYROGEN
FREE WATER
350 1 85 %
ALCOHOL
SUPER V
SYRUP V
176 KG ≡ 77.4 KG DEXTRIN

Fig. 3.

ETHANOL FRACTIONATION

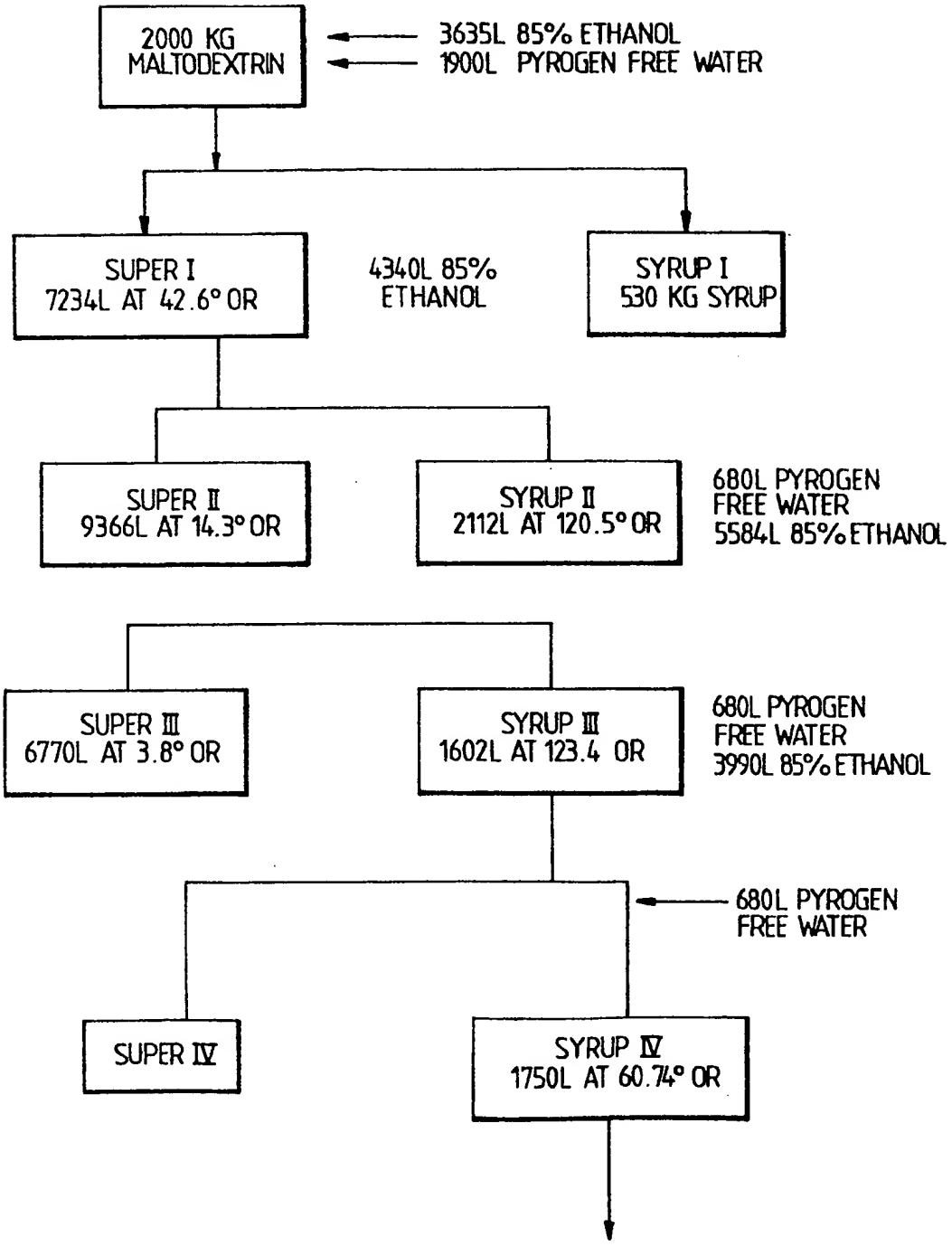


Fig.3.(cont).

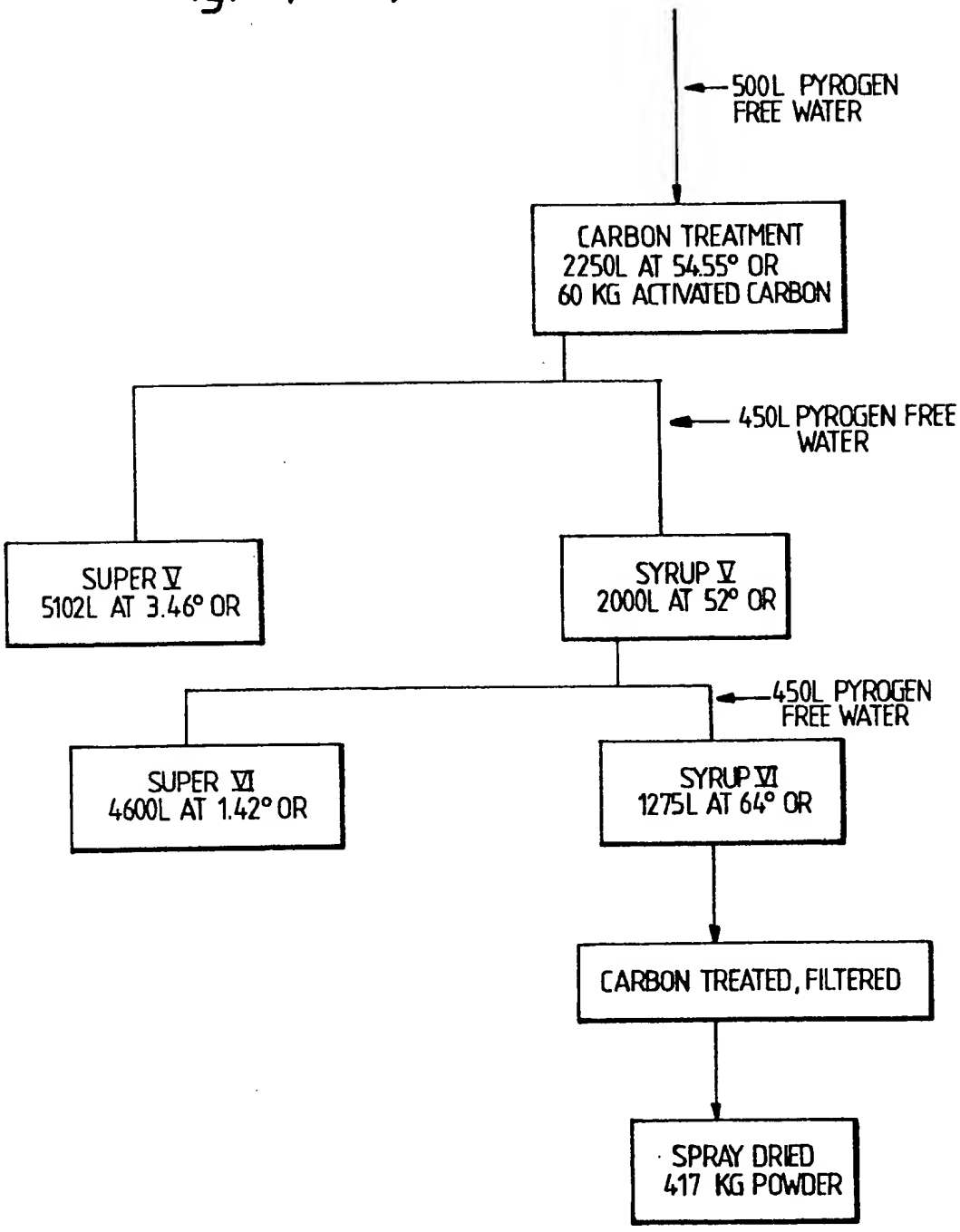

500L PYROGEN FREE WATER
CARBON TREATMENT 2250L AT 54.55° OR 60 KG ACTIVATED CARBON
450L PYROGEN FREE WATER
SUPER V 5102L AT 3.46° OR
SYRUP V 2000L AT 52° OR
450L PYROGEN FREE WATER
SUPER VI 4600L AT 1.42° OR
SYRUP VI 1275L AT 64° OR
CARBON TREATED, FILTERED
SPRAY DRIED 417 KG POWDER

Fig.4.

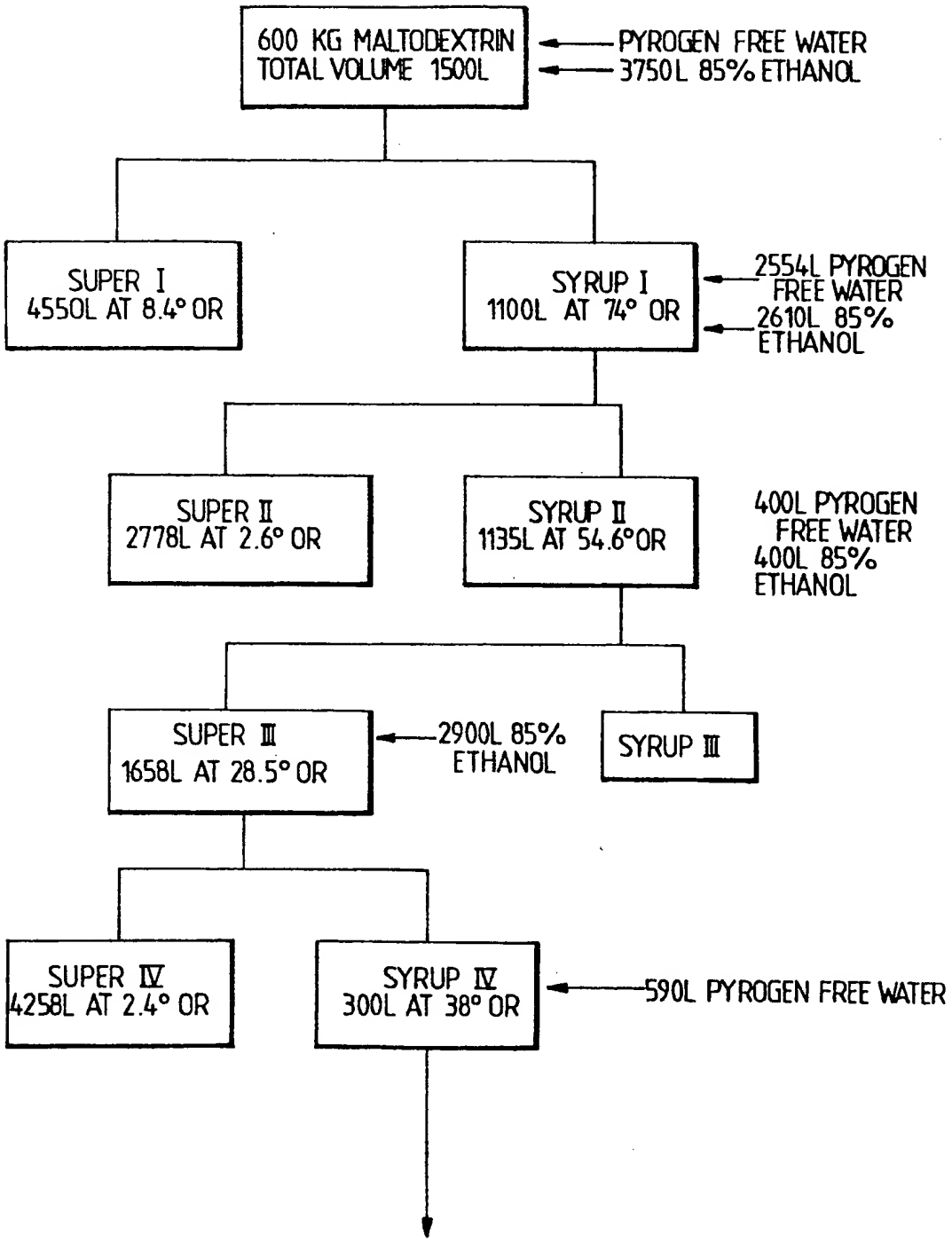

600 KG MALTODEXTRIN
TOTAL VOLUME 1500L
PYROGEN FREE WATER
3750L 85% ETHANOL
SUPER I
4550L AT 8.4° OR
SYRUP I
1100L AT 74° OR
2554L PYROGEN FREE WATER
2610L 85% ETHANOL
SUPER II
2778L AT 2.6° OR
SYRUP II
1135L AT 54.6°OR
400L PYROGEN FREE WATER
400L 85% ETHANOL
SUPER III
1658L AT 28.5° OR
2900L 85% ETHANOL
SYRUP III
SUPER IV
4258L AT 2.4° OR
SYRUP IV
300L AT 38° OR
590L PYROGEN FREE WATER

Fig.4.(cont).

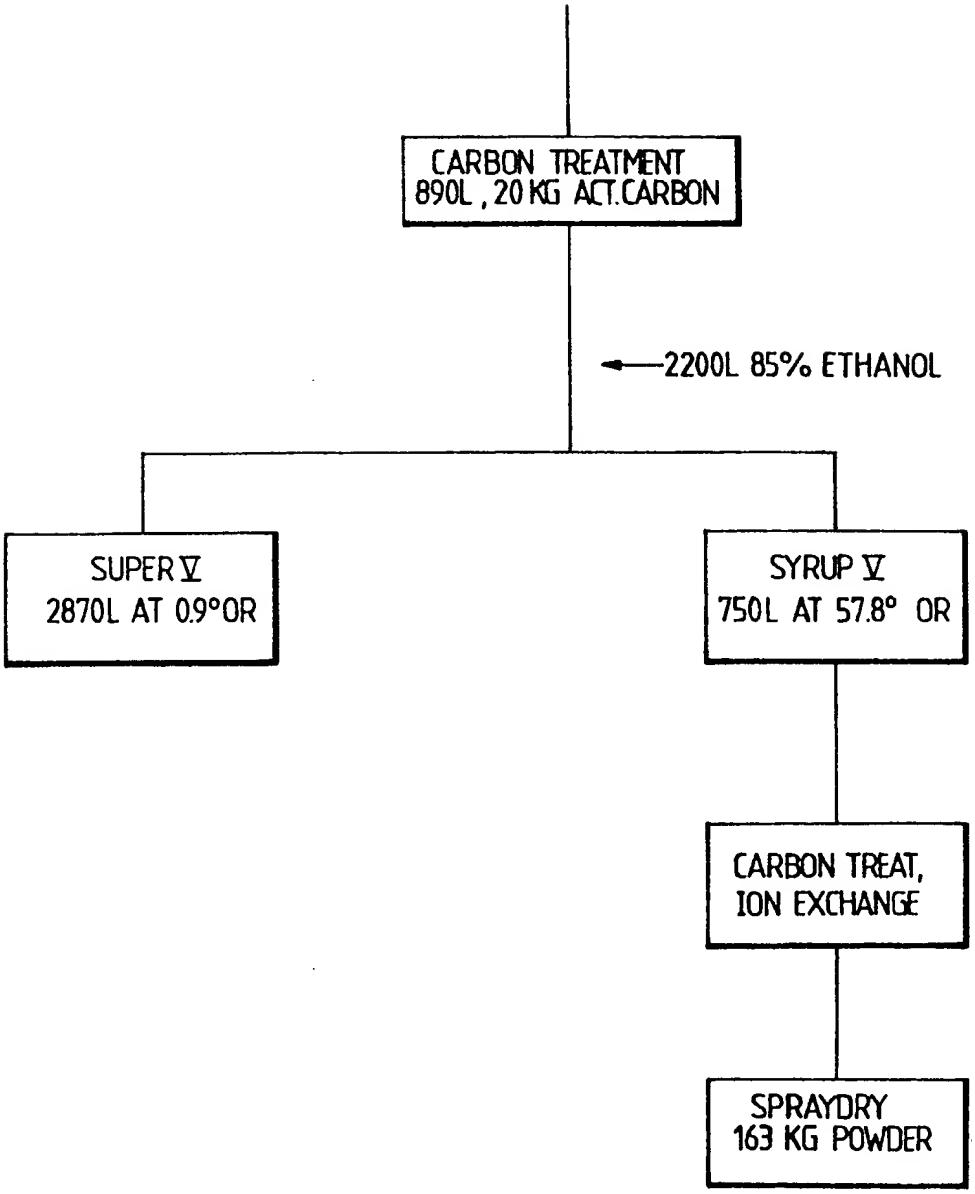
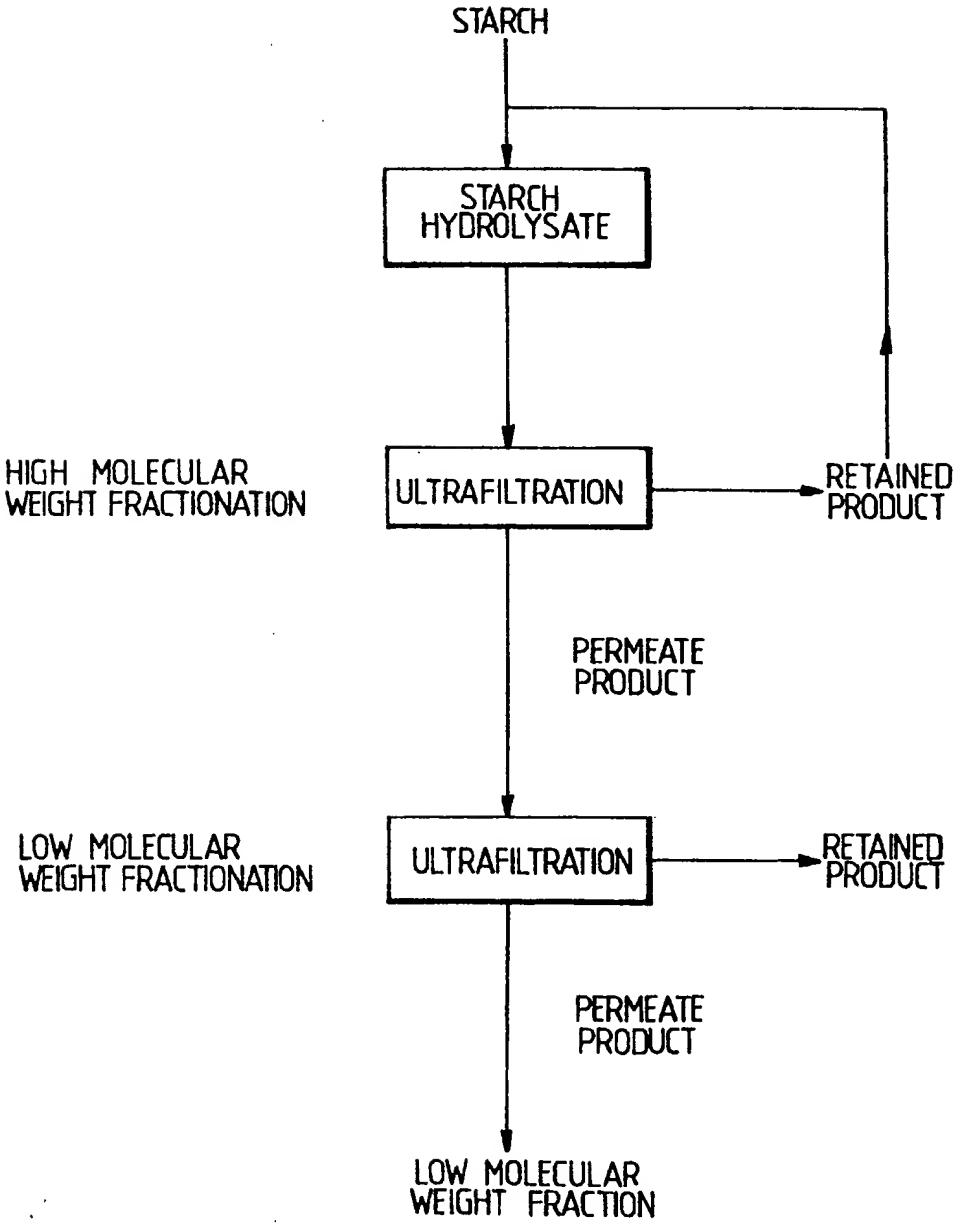

CARBON TREATMENT
890L, 20 KG ACT.CARBON
2200L 85% ETHANOL
SUPER V
2870L AT 0.9°OR
SYRUP V
750L AT 57.8° OR
CARBON TREAT,
ION EXCHANGE
SPRAYDRY
163 KG POWDER

Fig.5.


STARCH
STARCH HYDROLYSATE
HIGH MOLECULAR WEIGHT FRACTIONATION
ULTRAFILTRATION
RETAINED PRODUCT
PERMEATE PRODUCT
LOW MOLECULAR WEIGHT FRACTIONATION
ULTRAFILTRATION
RETAINED PRODUCT
PERMEATE PRODUCT
LOW MOLECULAR WEIGHT FRACTION

(19) Europäisches Patentamt
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A3

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C 13 K 1/06, A 61 M 1/28
A 61 K 31/715

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(71) Applicant: FISONS plc
Fison House Princes Street
Ipswich Suffolk IP1 1QH(GB)

(72) Inventor: Alsop, Ranulph Michael
28 Windemere Drive
Alderley Edge Cheshire(GB)

(72) Inventor: Forrester, Raymond Brian
7 Alderley Close
Sandbach Cheshire(GB)

(72) Inventor: Manning, David John
Hillview Under Rainow Road Timbersbrook
Congleton Cheshire(GB)

(74) Representative: Craig, Christopher Bradberry et al,
Fisons plc 12 Derby Road
Loughborough Leicestershire LE11 0BB(GB)

(54) **Polymers for use in continuous peritoneal dialysis.**

(57) There is described polysaccharides of high molecular weight for use in peritoneal dialysis. The polysaccharides are capable of dialysing human serum for long periods of time without causing damage to the peritoneum and are also capable of preventing loss of polymer from the peritoneum to the serum.

There is also described a method of making the polysaccharides and pharmaceutical formulations containing them.

EP 0 207 676 A3

Croydon Printing Company Ltd.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 86 30 4624

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	WO-A-8 203 329 (D. SILK et al.) * Example 1; table III; page 18, paragraph 2; claims * ---	1-10	C 08 B 30/18 C 13 K 1/06 A 61 M 1/28 A 61 K 31/715
P,X	EP-A-0 153 164 (MILNER LABORATORIES LTD) * Claims * ---	1-11	
X	CHEMICAL ABSTRACTS, vol. 85, 1976, page 410, abstract no. 141580f, Columbus, Ohio, US; & JP-A-76 88 645 (AJINOMOTO CO., INC.) 03-08-1976 * Whole document * ---	1	
A	CHEMICAL ABSTRACTS, vol. 99, 1983, page 619, abstract no. 105608b, Columbus, Ohio, US; S. KIKUMOTO et al.: "Naegeli amylodextrin. Large scale preparation of fractions by step-wise precipitation using organic solvents", & DENPUN KAGAKU 1983, 30(1), 69-75 -----		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 08 B
A 61 M
A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-01-1988	LENSEN H.W.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office uropéen d s brevets

(11) Publication number: **0 207 676 B1**

(12) # EUROPEAN PATENT SPECIFICATION

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(51) Int. Cl.[5]: **C08B 30/18**, C13K 1/06, A61M 1/28, A61K 31/715

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(22) Date of filing: **16.06.86**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Polymers for use in continuous peritoneal dialysis.**

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02.05.86 GB 8610841

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07.01.87 Bulletin 87/02

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(56) References cited:
EP-A- 0 153 164
WO-A-82/03329

CHEMICAL ABSTRACTS, vol. 85, 1976, page 410, abstract no. 141580f, Columbus,Ohio, US; & JP-A-76 88 645 (AJINOMOTO CO., INC.) 03-08-1976

CHEMICAL ABSTRACTS, vol. 99, 1983, page 619, abstract no. 105608b, Columbus,Ohio, US; S. KIKUMOTO et al.: "Naegeli amylodextrin. Large scale preparation of fractions by step-wise precipitation using organic solvents", & DENPUN KAGAKU, 30(1), 69-75

fractions by step-wise precipitation using organic solvents", & DENPUN KAGAKU1983, 30(1), 69-75

(73) Proprietor: **M L LABORATORIES PLC**
Marcol House, 293 Regent Street
London W1R 7PD(GB)

(72) Inventor: **Alsop, Ranulph Michael**
28 Windemere Drive
Alderley Edge Cheshire(GB)
Inventor: **Forrester, Raymond Brian**
7 Alderley Close
Sandbach Cheshire(GB)
Inventor: **Manning, David John**
Hillview
Under Rainow Road
Timbersbrook
Congleton Cheshire(GB)

(74) Representative: **Harrison, Michael Robert et al**
DIBB LUPTON BROOMHEAD and PRIOR
117 The Headrow
Leeds LS1 5JX (GB)

EP 0 207 676 B1

Table 11

Molecular Weight Distribution	
MOLECULAR WEIGHTS	INTEGRAL DISTRIBUTION
170	0.00
845	2.50
1292	5.00
1674	7.50
2044	10.00
2429	12.50
2841	15.00
3283	17.50
3754	20.00
4269	22.50
4805	25.00
5361	27.50
5958	30.00
6583	32.50
7232	35.00
7937	37.50
8666	40.00
9447	42.50
10273	45.00
11129	47.50
12062	50.00
13024	52.50
14053	55.00
15147	57.50
16281	60.00
17537	62.50
18860	65.00
20264	67.50
21839	70.00
23542	72.50
25408	75.00
27488	77.50
29900	80.00
32694	82.50
36020	85.00
40183	87.50
45419	90.00
52731	92.50
64063	95.00
85249	97.50
349210	100.00

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A peritoneal dialysis composition containing an osmotic agent which is a mixture of glucose polymers, wherein at least 50% by weight of the mixture comprises polymers having molecular weights in the range of from 5,000 to 30,000, and wherein the mixture has a weight average molecular weight of from 5,000 to 50,000 and a number average molecular weight of from 2,900 to 8,000, both the weight average molecular weight and the number average molecular weight being determined using chromatographic columns calibrated with dextran standards (Alsop et al, Process Biochem [2], 10-15

(1977) and Alsop et al, J. Chromatography, [246], 227-240 (1982)).

2. A composition according to claim 1, wherein the mixture of glucose polymers contains less than 5% by weight of polymers of molecular weight greater than 100,000.

3. A composition according to claim 1 or claim 2, wherein the mixture of glucose polymers contains no more than 20% by weight of polymers having molecular weights of from 800 to 10,000.

4. A composition according to any one of the preceding claims, additionally comprising a pharmaceutically acceptable adjuvant, diluent or carrier.

Claims for the following Contracting State : AT

1. A process for the preparation of a physiologically acceptable polysaccharide, being a mixture of glucose polymers, wherein at least 50% by weight of the mixture comprises polymers having molecular weights in the range of from 5,000 to 30,000, and wherein the mixture has a weight average molecular weight of from 5,000 to 50,000 and a number average molecular weight of from 2,900 to 8,000, both the weight average molecular weight and the number average molecular weight being determined using chromatographic columns calibrated with dextran standards (Alsop et al, Process Biochem [2], 10-15 (1977) and Alsop et al, J. Chromatography, [246], 227-240 (1982)), characterised in that the process comprises:
   (a) fractional precipitation of an aqueous solution of a polymer with a water miscible solvent, and/or
   (b) filtration of an aqueous solution of a polymer through membranes possessing an appropriate molecular weight cut-off range.

2. A process according to Claim 1, wherein the polysaccharide has a content of glucose polymers with molecular weight greater than 100,000 of less than 5% by weight.

3. A process according to Claim 1 or Claim 2, wherein the polysaccharide has up to 20% by weight of its molecules of a molecular weight of from 800 to 10,000.

4. A process according to any one of the preceding claims, wherein the polysaccharide is admixed with a pharmaceutically acceptable adjuvant, diluent or carrier to provide a composition which is capable of dialysing normal human serum.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Eine Peritonealdialyse-Zusammensetzung, die ein osmotisches Mittel enthält, welches eine Mischung von Glukosepolymeren ist, wobei mindestens 50 Gewichts-% der Mischung Polymere mit Molekulargewichten im Bereich von 5000 bis 30000 enthält und wobei die Mischung ein Durchschnittsgewicht des Molekulargewichts von 5000 bis 50000 und eine Durchschnittszahl des Molekulargewichts von 2900 bis 8000 besitzt, wobei sowohl das Durchschnittsgewicht des Molekulargewichts und die Durchschnittszahl des Molekulargewichts mit chromatographischen Säulen bestimmt wird, die mit Dextran Standards geeicht worden sind (Alsop et al, Process Biochem. [2], 10-15 (1977) und Alsop et al., J. Chromatography, [246], 227-240 (1982)).

2. Eine Zusammensetzung nach Anspruch 1, in der die Mischung der Glukosepolymere weniger als 5 Gewichts-% an Polymeren mit einem Molekulargewicht größer als 100000 enthält.

3. Eine Zusammensetzung nach Anspruch 1 oder Anspruch 2, in der die Mischung der Glukosepolymere nicht mehr als 20 Gewichts-% an Polymeren mit Molekulargewichten von 800 bis 10000 enthält.

4. Eine Zusammensetzung nach einem der vorhergehenden Ansprüchen, die zusätzlich ein pharmazeutisch annehmbares Adjuvans, ein Verdünnungsmittel oder einen Träger enthält.

Patentansprüche für folgenden Vertragsstaat : AT

1. Ein Verfahren für die Herstellung eines physiologisch annehmbaren Polysaccharids, der eine Mischung von Glukosepolymeren ist, wobei mindestens 50 Gewichts-% der Mischung Polymere enthält, die Molekulargewichte im Bereich von 5000 bis 30000 besitzen, und wobei die Mischung ein Durchschnittsgewicht des Molekulargewichts von 5000 bis 50000 besitzt und eine Durchschnittszahl des Molekulargewichts von 2900 bis 8000, wobei sowohl das Durchschnittsgewicht des Molekulargewichts als auch die Durchschnittszahl des Molekulargewichts mit Hilfe von chromatographischen Säulen bestimmt wird, die mit Dextran Standards geeicht worden sind (Alsop et al., Process Biochem [2], 10-15 (1977) und Alsop et al., J. Chromatography [246], 227-240 (1982)), charakterisiert dadurch, daß das Verfahren beinhaltet:
   (a) die fraktionelle Fällung einer wäßrigen Lösung eines Polymers mit einem wassermischbaren Lösungsmittel, und/oder
   (b) die Filtration einer wäßrigen Lösung eines Polymers durch Membranen, die einen geeigneten Molekulargewicht-Rückhaltevermögensbereich besitzen.

2. Ein Verfahren nach Anspruch 1, in dem der Polysaccharid einen Inhalt von weniger als 5 Gewichts-% an Glukosepolymeren mit einem Molekulargewicht größer als 100000 besitzt.

3. Ein Verfahren nach Anspruch 1 oder Anspruch 2, in dem der Polysaccharid bis zu 20 Gewichts-% seiner Moleküle mit einem Molekulargewicht von 800 bis 10000 besitzt.

4. Ein Verfahren nach einem der vorhergehenden Ansprüche, in dem der Polysaccharid mit einem pharmazeutisch annehmbaren Adjuvans, einem Verdünnungsmittel oder einem Träger vermischt ist, um eine Zusammensetzung zur Verfügung zu stellen, die fähig ist, normales menschliches Serum zu dialysieren.

Revendications
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Une composition pour dialyse péritonéale contenant un agent osmotique qui est un mélange de polymères de glucose, dans laquelle au moins 50% de la masse du mélange comprend des polymères ayant des masses moléculaires dans la plage comprise entre 5.000 et 30.000, et dans laquelle le mélange a une masse moléculaire moyenne entre 5.000 et 50.000 et un nombre de masse moléculaire moyenne entre 2.900 et 8.000, la masse moléculaire moyenne et le nombre de masse moléculaire moyenne étant tous deux déterminés à l'aide de colonnes de chromatographie étalonnées avec des standards de dextranes (Alsop et al, Process Biochem (2), 10-15 (1977) et Alsop et al, J. Chromatography, (246), 227-240 (1982)).

2. Une composition selon la revendication 1, dans laquelle le mélange de polymères de glucose contient moins de 5% en masse de polymères de masse moléculaire supérieure à 100.000.

3. Une composition selon l'une des revendications 1 et 2, dans laquelle le mélange de polymères de glucose ne contient pas plus de 20% en masse de polymères ayant des masses moléculaires entre 800 et 10.000.

4. Une composition selon l'une quelconque des revendications précédentes, comprenant en outre un adjuvant, diluant ou porteur pharmaceutiquement compatible.

Revendications pour l'Etat contractant suivant : AT

1. Un procédé pour la préparation d'un polysaccharide physiologiquement compatible, étant un mélange de polymères de glucose, dans lequel au moins 50% de la masse du mélange comprend des polymères ayant des masses moléculaires dans la plage comprise entre 5.000 et 30.000, et dans lequel le mélange a une masse moléculaire moyenne comprise entre 5.000 et 50.000 et un nombre de masse moléculaire moyenne entre 2.900 et 8.000, la masse moléculaire moyenne et le nombre de masse moléculaire moyenne étant tous deux déterminés à l'aide de colonnes de chromatographie étalonnées avec des standards de dextranes (Alsop et al, Process Biochem (2), 10-15 (1977) et Alsop

et al, J. Chromatography, (246), 227-240 (1982)), caractérisé en ce que le procédé comporte:

(a) une précipitation fractionnée d'une solution aqueuse d'un polymère avec un solvant miscible à l'eau, et/ou

(b) une filtration d'un solution aqueuse d'un polymère à travers des membranes possédant une plage d'arrêt de masses moléculaires appropriée.

2. Un procédé selon la revendication 1, dans lequel le polysaccharide a une quantité de polymères de glucose avec une masse moléculaire supérieure à 100.000, inférieure à 5% en masse.

3. Un procédé selon l'une des revendications 1 et 2, dans lequel le polysaccharide a jusqu'à 20% en masse de ses molécules d'une masse moléculaire entre 800 et 10.000.

4. Un procédé selon l'une quelconque des revendications précédentes, dans lequel le polysaccharide est mélangé avec un adjuvant, diluant ou porteur pharmaceutiquement compatible pour obtenir une composition apte à dialyser un sérum humain normal.